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(71) Applicant: **WYETH** [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US).

(72) Inventors: **DUKART, Gary**; 1714 Benjamin Drive, Ambler, PA 19002 (US). **GIBBONS, James, Joseph, Jr.**; 33 Terrace Drive, Westwood, NJ 07675 (US). **SPEICHER, Lisa, Anne**; 509 Covington Road, Havertown, PA 19083 (US). **FROST, Philip**; 4 Emerson Court, Morris Township, NJ 07960 (US). **DISCAFANI-MARRO, Carolyn, Mary**; 8 Brookside Avenue, Cortlandt Manor, NY 10567 (US).

(74) Agents: **MILOWSKY, Arnold, S.**; Wyeth, Patent Law Department, Five Giralda Farms, Madison, NJ 07940-0874 et al. (US).

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(54) Title: **USE OF CCI-779 AS AN ANTINEOPLASTIC AGENT**

(57) Abstract: This invention provides the use of CCI-779 in the treatment of neoplasms.

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### USE OF CCI-779 AS AN ANTINEOPLASTIC AGENT

This invention relates to the use of rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) as an antineoplastic agent.

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Rapamycin is a macrocyclic triene antibiotic produced by Streptomyces hygroscopicus, which was found to have antifungal activity, particularly against Candida albicans, both in vitro and in vivo [C. Vezina et al., J. Antibiot. 28, 721 (1975); S.N. Sehgal et al., J. Antibiot. 28, 727 (1975); H. A. Baker et al., J. Antibiot. 31, 539 (1978); U.S. Patent 3,929,992; and U.S. Patent 3,993,749]. Additionally, rapamycin alone (U.S. Patent 4,885,171) or in combination with picibanil (U.S. Patent 4,401,653) has been shown to have antitumor activity.

The immunosuppressive effects of rapamycin have been disclosed in FASEB 3, 3411 (1989). Cyclosporin A and FK-506, other macrocyclic molecules, also have been shown to be effective as immunosuppressive agents, therefore useful in preventing transplant rejection [FASEB 3, 3411 (1989); FASEB 3, 5256 (1989); R. Y. Calne et al., Lancet 1183 (1978); and U.S. Patent 5,100,899]. R. Martel et al. [Can. J. Physiol. Pharmacol. 55, 48 (1977)] disclosed that rapamycin is effective in the experimental allergic encephalomyelitis model, a model for multiple sclerosis; in the adjuvant arthritis model, a model for rheumatoid arthritis; and effectively inhibited the formation of IgE-like antibodies.

Rapamycin is also useful in preventing or treating systemic lupus erythematosus [U.S. Patent 5,078,999], pulmonary inflammation [U.S. Patent 5,080,899], insulin dependent diabetes mellitus [U.S. Patent 5,321,009], skin disorders, such as psoriasis [U.S. Patent 5,286,730], bowel disorders [U.S. Patent 5,286,731], smooth muscle cell proliferation and intimal thickening following vascular injury [U.S. Patents 5,288,711 and 5,516,781], adult T-cell leukemia/lymphoma [European Patent Application 525,960 A1], ocular inflammation [U.S. Patent 5,387,589], malignant carcinomas [U.S. Patent 5,206,018], cardiac inflammatory disease [U.S. Patent 5,496,832], and anemia [U.S. Patent 5,561,138].

The preparation and use of hydroxyesters of rapamycin, including CCI-779, are disclosed in U.S. Patent 5,362,718.

#### DESCRIPTION OF THE INVENTION

5        This invention provides the use of CCI-779 as an antineoplastic agent, and particularly for neoplasms which are refractory to standard therapy, or for whom standard therapy is not appropriate. In particular CCI-779 is useful in the treatment of renal cancer, soft tissue cancer, breast cancer, neuroendocrine tumor of the lung, cervical cancer, uterine cancer, head and neck cancer, glioblastoma, non-small lung  
10 cell cancer, prostate cancer, pancreatic cancer, lymphoma, melanoma, small cell lung cancer, ovarian cancer, colon cancer.

As used in accordance with this invention, the term "treatment" means treating a mammal having a neoplastic disease by providing said mammal an effective amount  
15 of CCI-779 with the purpose of inhibiting growth of the neoplasm in such mammal, eradication of the neoplasm, or palliation of the neoplasm.

As used in accordance with this invention, the term "providing," with respect to providing CCI-779, means either directly administering CCI-779, or administering  
20 a prodrug, derivative, or analog which will form an effective amount of CCI-779 within the body.

As used in accordance with this invention, the term "refractory neoplasm" refers to neoplasms in patients which typically had progressed following treatment  
25 with standard chemotherapy that was appropriate for that given neoplasm.

The preparation of CCI-779 is described in U.S. Patent 5,362,718, which is hereby incorporated by reference.

30        The antineoplastic activity of CCI-779 was confirmed in a preclinical *in vitro* and *in vivo* standard pharmacological test procedure which measured the ability of

CCI-779 to treat human renal cell cancer (a rapidly progressive disease with very limited treatment options), as well as in two Phase I human clinical trials. The procedures used and results obtained are briefly described below.

5    Preclinical Test Procedures

10        In vitro test procedure: Renal tumor lines HTB-44 and CRL-1161 were obtained from the American Tissue Culture Collection (ATCC), Bethesda, MD. SN12-C line was obtained from Dr. J. Fidler, M.D. Anderson Hospital, Houston, TX. Cells were plated in MEM (Gibco) supplemented with 2 mM glutamine, 1 mM sodium pyruvate, 5 ml penicillin-streptomycin solution, 1 mM non-essential amino acid solution, 10% fetal bovine solution. Cells ( $5 \times 10^3$ ) were plated in 96 well plates with a final volume of 200 ml and incubated for 24 hours at 37°C. Log dilutions of CCI-779 beginning at 100 µg/ml were then added to the cultures for 48 hours. Over the last 5 hours, cells were pulsed with 1 µci  $^3\text{H}$ -thymidine (New England Nuclear, 15    6.7 ci/m Mol). Cells were then harvested and the degree of thymidine uptake determined by liquid scintillation spectrometry. The  $\text{IC}_{50}$  was determined as the concentration that produced 50% of the maximum uptake of thymidine in control untreated cells.

20        In vivo test procedure: Female Balb/c nu/nu mice were obtained from Charles River Labs, Wilmington, DE, at 6-8 weeks of age. Mice (n=10/group) were injected sc with  $5 \times 10^6$  cells resuspended in a 50% solution of Matrigel (BD Biosciences) and tumors allowed to develop. When tumor size reached 100 mg, mice were treated orally with CCI-779 at 25 mg/kg. CCI-779 was dosed for 5 consecutive days with 25    repeated 14 day cycles throughout the duration of the experiment. The formulation used for CCI-779 was a 50% ethanol, 49% phosal, 1% tween 80 vehicle for resuspending CCI-779, where the stock was resuspended into a 1:10 dilution of the vehicle prior to dosing. Tumor growth was evaluated using a vernier caliper and volume ( $l \times w \times h$ ) was converted to mass using the formula:  $l \times w^2 / 2$ .

30

Results:

Human renal cell tumors were cultured *in vitro* in the presence or absence of CCI-779 for 3 days and the effect on growth determined by <sup>3</sup>H-thymidine incorporation of control versus treated cells. Table 1 shows that IC<sub>50</sub> (50% growth inhibitory concentration) for all 3 lines tested was in the low nM range.

Table 1 The effect of CCI-779 on the growth of human renal tumor cells *in vitro*

<u>Renal Tumor Line</u>	<u>CCI-779 IC<sub>50</sub> (nM)</u>
HTB-44	5.0
CRL-1161	2.0
SN12-C	5.5

10

The effect of CCI-779 in two human renal lines (HTB-44 and CRL-1161) were was evaluated *in vivo* by engrafting tumor cells on the flanks of nude mice. Once tumors were established at a size of about 100 mg, mice were treated with CCI-779 or a vehicle control. Treatment with CCI-779 at 25 mg/kg resulted in significant inhibition of tumor cell growth in the mice (Table 2).

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Table 2 Effect of CCI-779 on the growth of human renal tumor cells in nude mouse xenografts

Cell Line	Drug Treatment	Tumor Mass (mg)					
		Days					
		0	7	21	35	49	55
HTB-44	Control	288±21	219±18	616±55	1095±44	2033±247	2412±342
	CCI	290±15	156±13*	252±48*	453±85*	980±155*	1050±183*
	% T/C	101	71	41	41	48	44
CRL-1161	Control	273±18	355±36	413±60	480±127	546±170	507±156
	CCI	272±14	219±16*	226±17*	200±21*	229±28*	268±30
	% T/C	100	62	60	42	42	53

20

\* p value - &lt; .05

% T/C - Treated/Control x 100

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Clinical Trial:

Two single agent (CCI-779) Phase I clinical trials have been conducted. In the first study, CCI-779 was administered as a 30 minute i.v. infusion daily for 5 days, every two to three weeks. In the second study, CCI-779 was administered as a 30 minute i.v. infusion, once weekly. Both trials were open label, ascending dose, single-arm, multicenter studies. Patients were allowed to continue treatment as long as the CCI-779 was tolerated and there was no evidence of obvious disease progression. The following eligibility criteria were used:

Inclusion Criteria

- 10 1. Patients with a histologic diagnosis of advanced cancer (solid tumors and, in the first study, lymphomas) who are refractory to standard therapy or for whom standard therapy is not appropriate.
2. Measurable or evaluable disease.
3. At least 3 weeks since prior chemotherapy and/or radiation therapy (6 weeks since nitrosoureas or mitomycin C).
- 15 4. At least 4 weeks since any other investigational agent.
5. Age at least 18 years old.
6. Adequate bone marrow, renal, and hepatic function.
7. Serum cholesterol  $\leq 350$  mg/dL and triglycerides  $\leq 300$  mg/dL.
- 20 8. ECOG performance status 0-2.
9. Life expectancy of at least 3 months.
10. Signed, dated, witnessed written informed consent.

A total of 63 patients and 24 patients were enrolled in first and second studies, respectively. Dose levels ranged from 0.75-24 mg/m<sup>2</sup> and 7.5-220 mg/m<sup>2</sup>, with the daily x 5 every 2 weeks and weekly schedules, respectively.

The following summarizes the results that were obtained:

In patients having renal cancer on the weekly schedule, 1 partial response ( $\geq$  50% reduction in tumor size) and 2 minor responses ( $\geq 25\%$  but  $< 50\%$  reduction in

tumor size) were observed. In renal cancer patients on the daily x 5 schedule, 1 minor response, 1 unconfirmed minor response, and 1 stable disease (< 25% increase to < 25% reduction in tumor size) lasting approximately 5 months were observed. In patients having soft tissue sarcoma on the daily x 5 dosage schedule, 1 possible partial response, 2 minor responses, and 1 stable disease lasting approximately 5½ months were observed. In patients with breast cancer on the weekly dosage schedule, one partial response was observed. In patients with neuroendocrine tumor of the lung on the weekly dosage schedule, one partial response was observed. In patients having cervical cancer on the daily x 5 dosage schedule, one minor response was observed. In patients having uterine cancer receiving the daily x 5 dosage schedule, one unconfirmed minor response was observed. In patients having head and neck cancer receiving the daily x 5 dosage schedule, 1 stable disease for approximately 8½ months was observed. In patients having non-small cell lung cancer receiving the daily x 5 dosage schedule, one partial response was observed. These results are particularly surprising, considering that the patients in these studies had advanced cancers that were generally refractory to standard treatment, and also considering that these were Phase I clinical trials, in which efficacy is often limited, as the primary objective of a Phase I trial is to determine the safety and tolerability of the drug being evaluated.

Based on the results of the preclinical and clinical test procedures, CCI-779 is useful in treating neoplasms, in particular, refractory neoplasms. More particularly, CCI-779 is useful in treating treatment of renal carcinoma, soft tissue carcinoma, breast cancer, neuroendocrine tumor of the lung, cervical cancer, uterine cancer, head and neck cancer, glioblastoma, non-small cell lung cancer, prostate cancer, pancreatic cancer, lymphoma, melanoma, small cell lung cancer, ovarian cancer, and colon cancer.

As typical with chemotherapy, dosage regimens are closely monitored by the treating physician, based on numerous factors including the severity of the disease, response to the disease, any treatment related toxicities, age, and health of the patient.

Based on the results obtained with CCI-779, it is projected that initial i.v. infusion dosages will be between about 0.1 and 100 mg/m<sup>2</sup> when administered on a daily dosage regimen, and between about 1 and 1000 mg/m<sup>2</sup> when administered on a weekly dosage regimen. Other dosage regimens and variations are foreseeable, and will be determined through physician guidance. It is preferred that CCI-779 is administered by i.v. infusion or orally, preferably in the form of tablets or capsules. Other routes of administration are also feasible, such as via implants, parenterally (besides i.v., such as intraperitoneal and subcutaneous injections), rectally, intranasally, vaginally, and transdermally.

10 Dosage regimens are expected to vary according to the route of administration. For example, dosages for oral administration are often up to tenfold greater than for i.v. administration. It is anticipated that CCI-779 may be administered as the sole active chemotherapeutic agent, or may be part of a chemotherapeutic regimen containing more than one antineoplastic agent. The use of concomitant  
15 chemotherapeutic agents often allows for dosage reduction of each particular agent, thereby increasing the safety margin of the particular agents.

Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may  
20 contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation  
25 methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate,  
30 complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium



phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Preferred surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium  
5 stearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). The oral formulation may also consist of administering the active ingredient in water or a fruit  
10 juice, containing appropriate solubilizers or emulsifiers as needed.

In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

The compounds of this invention may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base  
15 or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

20 The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the  
25 contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

For the purposes of this disclosure, transdermal administrations are  
30 understood to include all administrations across the surface of the body and the inner

linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

- 5 Transdermal administration may be accomplished through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices.
- 10 The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semi-permeable membrane covering a reservoir
- 15 containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

- Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of
- 20 various molecular weights, may also be used.

CLAIMS

1. A method of treating a neoplasm in a mammal in need thereof, which comprises providing to said mammal an effective amount of CCI-779.
- 5
2. A method of treating a refractory neoplasm in a mammal in need thereof, which comprises providing to said mammal an effective amount of CCI-779.
3. The method according to claim 1, wherein the neoplasm is renal cancer.
- 10
4. The method according to claim 1, wherein the neoplasm is soft tissue sarcoma.
5. The method according to claim 1, wherein the neoplasm is breast cancer.
- 15
6. The method according to claim 1, wherein the neoplasm is a neuroendocrine tumor of the lung.
7. The method according to claim 1, wherein the neoplasm is cervical cancer.
- 20
8. The method according to claim 1, wherein the neoplasm is uterine cancer.
- 25
9. The method according to claim 1, wherein the neoplasm is a head and neck cancer.
10. The method according to claim 1, wherein the neoplasm is glioblastoma.
- 30

11. The method according to claim 1, wherein the neoplasm is non-small cell lung cancer.
- 5 12. The method according to claim 1, wherein the neoplasm is prostate cancer.
13. The method according to claim 1, wherein the neoplasm is pancreatic cancer.
- 10 14. The method according to claim 1, wherein the neoplasm is lymphoma.
15. The method according to claim 1, wherein the neoplasm is melanoma.
- 15 16. The method according to claim 1, wherein the neoplasm is small cell lung cancer.
17. The method according to claim 1, wherein the neoplasm is ovarian cancer.
- 20 18. The method according to claim 1, wherein the neoplasm is colon cancer.
- 25 19. Use of rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) in the preparation of a medicament for the treatment of a neoplasm in a mammal.
- 30 20. Use of rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) in the preparation of a medicament for the treatment of a refractory neoplasm in a mammal.

21. Use according to claim 19 wherein the neoplasm is renal cancer, soft tissue sarcoma, breast cancer, neuroendocrine tumor of the lung, cervical cancer, uterine cancer, head and neck cancer, glioblastoma, non-small cell lung cancer,
- 5 prostate cancer, pancreatic cancer, lymphoma, melanoma, small cell lung cancer, ovarian cancer or colon cancer.

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CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

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(57) Abstract: This invention provides the use of CCI-779 in the treatment of neoplasms.

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# INTERNATIONAL SEARCH REPORT

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**A. CLASSIFICATION OF SUBJECT MATTER**  
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## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

MEDLINE, BIOSIS, EMBASE, EPO-Internal, WPI Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	GEOERGER BIRGIT ET AL: "Antitumor activity of the rapamycin analog CCI-779 in human primitive neuroectodermal tumor/medulloblastoma models as single agent and in combination chemotherapy." CANCER RESEARCH, vol. 61, no. 4, 15 February 2001 (2001-02-15), pages 1527-1532, XP001079526 ISSN: 0008-5472 the whole document --- -/--	1-21

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax (+31-70) 340-3016

Authorized officer

Brück, M



## INTERNATIONAL SEARCH REPORT

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>GEOERGER, B KERR, K. JANSS, AJ. SUTTON LN. PHILLIPS PC.: "rapamycin analog cci 779 inhibits growth of human medulloblastoma xenografts"</p> <p>PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 40, March 1999 (1999-03), XP001080186 the whole document</p>	1-21
X	<p>ALEXANDRE, JEROME ET AL.: "Phase I study of CCI-779, a novel rapamycin analog: preliminary results"</p> <p>PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 41, March 1999 (1999-03), page 613 XP001071217 page 613</p>	1-21
X	<p>GIBBONS J J ET AL: "The effect of CCI-779, a novel macrolide anti-tumor agent, on the growth of human tumor cells in vitro and in nude mouse xenografts in vivo."</p> <p>PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 40, March 1999 (1999-03), page 301 XP001071222</p> <p>90th Annual Meeting of the American Association for Cancer Research; Philadelphia, Pennsylvania, USA; April 10-14, 1999, March, 1999 ISSN: 0197-016X page 301</p>	1-21
X	<p>ALEXANDRE, JEROME, RAYMOND, ERIC, ARMAND, JEAN-PIERRE: "La rapamycine et le CCI-779"</p> <p>BULLETIN DU CANCER, vol. 86, no. 10, October 1999 (1999-10), pages 808-811, XP001078856 page 810</p>	1-21
X	<p>SCHWARTSMANN, GILBERTO: "Marine organisms and other novel natural sources of new cancer drugs"</p> <p>ANNALS OF ONCOLOGY, vol. 11, no. 3, 13 October 2000 (2000-10-13), pages 235-243, XP001070989 page 239</p>	1-21

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 01/47324

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-18  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.1

Claims Nos.: 1-18

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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